REMARKS

Claim 1-6, 8, 10-18, 20, 22-24, 26-29, 31-34 are pending in this application. Claims 1 and 12 have been amended. Claim 13 has been canceled. Support for the amendments is found in the specification and claims as filed.

Interview

Applicants thank Examiner Isis Ghali for the courteous and helpful interview conducted with Applicants' representatives, Drew S. Hamilton and Gregory A. Hermanson, on October 27, 2005.

Claim Rejection 35 U.S.C. § 112, First Paragraph

Claim 1-6, 8, 10-18, 20, 22-24, 26-29, 31-34 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Although Applicants do not agree with the propriety of the rejection, independent claims 1 and 12 have been amended to remove "stable" from the claim language, solely to facilitate prosecution of these claims. Applicants reserve the ability to pursue claims directed to a "stable" liquid adhesive in one or more continuing patent applications. The remaining rejected claims are dependent upon independent Claims 1 or 12. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejection 35 U.S.C. § 103(a)

Claims 1, 4, 5, 8, 12, 13, 16, 17, 20, 26-29, and 31-34 have been rejected under 35 U.S.C. § 103(a) as unpatentable over WO 96/10,374 (hereinafter "WO '374") in view of U.S. Patent number 4,919,939 (hereinafter "US '939") To articulate a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the PTO must, *inter alia*, cite prior art that teaches or suggests all the claimed limitations. *In re Royka*, 490 F.3d 982 (C.C.P.A. 1974); MPEP §2143.03.

As discussed below, the cited references do not teach a liquid adhesive comprising, *inter alia*, a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent, "wherein the microcapsule comprises a protective shell configured to block chemical reaction between the antibiotic and the cyanoacrylate by substantially preventing direct contact of the antibiotic and the cyanoacrylate, whereby substantial premature curing of the adhesive prior to application is prevented, and wherein the microcapsule is configured to provide controlled release of antibiotic from the cured cyanoacrylate matrix" (Claim 1); or a method of sealing a wound comprising, *inter alia*, the steps

of "applying a liquid adhesive comprising a liquid mixture of a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a water soluble defect forming agent to a tissue surface surrounding the wound, wherein the microcapsule comprises a protective shell configured to block chemical reaction between the antibiotic and the cyanoacrylate by substantially preventing direct contact of the antibiotic and the cyanoacrylate" and "delivering the antibiotic to the wound through the defects in the cured adhesive at a controlled rate, wherein the microcapsule is configured to provide controlled release of the antibiotic from the cured adhesive" (Claim 12).

WO '374 teaches an adhesive composition comprising cyanoacrylate, PEG (a pore forming agent), and an active substance, *e.g.*, an antibiotic. US '939 teaches a controlled release drug delivery system for placement in a cavity within the mouth, comprising a plurality of microparticles suspended in a pharmaceutically acceptable carrier. A variety of methods are disclosed for preparing various types of microparticles. The types of microparticles include gelatin microcapsules prepared using a coacervation method, and microparticles comprising an eroding matrix comprising, *e.g.*, a cyanoacrylate containing a dispersion of large or unstable molecules. Regarding the erosion control system, it is noted that "[t]he agent does not diffuse through the polymer to any significant extent, and is thus essentially immobilized in the matrix until release by degradation of the surrounding material." The microparticles are delivered in a carrier medium which has, *inter alia*, "a low solubility but a high permeability to the drug in question." Examples of carrier fluids include water, aqueous solutions, syrups, alcohols, glycerin, mineral oil, vegetable oils, synthetic mucilage-like substances, and the like

As noted in the Office Action, WO '374 does not teach encapsulating the active substance. As also noted in the Office Action, US '939 is relied on solely for the teaching of microencapsulation of the active agent for controlled release.

Applicants have surprisingly discovered that cyanoacrylate adhesive formulations that maintain their liquid state until applied to a wound, and that maintain their antibiotic activity after curing such that the antibiotic can be delivered to the wound in a controlled release fashion, can be prepared by adding antibiotic encapsulated in a microcapsule to the cyanoacrylate along with a pore forming agent. The microcapsule prevents direct contact of the antibiotic and the cyanoacrylate, thereby 1) preventing premature curing (polymerization and solidification) of the

cyanoacrylate by the antibiotic; and 2) permitting controlled release of the antibiotic from the cured cyanoacrylate adhesive through defects in the cured adhesive provided by solvation of the defect forming agent. The cited references, alone or in combination, do not teach or suggest these two features of the liquid adhesives as claimed.

As Applicants have demonstrated by the experiments described in the Declaration of Yong-Hua Zhu submitted with the response to the previous Office Action, an antibiotic (when unencapsulated) reacts with cyanoacrylate upon contact, resulting in immediate premature polymerization and solidification of the cyanoacrylate. The problem of premature curing is neither identified nor addressed in either WO '374 or US '939, and there is no teaching or suggestion in either reference that whether the antibiotic was encapsulated or unencapsulated would have an impact on whether the form of the composition would be liquid or solid, and thus whether it was suitable for use as an adhesive, or whether the form of the antibiotic could impact the antibiotic effectiveness of the resulting composition. Neither reference teaches or suggests the desirability of adding antibiotic in microencapsulated form to obtain a liquid cyanoacrylate adhesive, instead of the solid compositions of WO '374 and US '939. Accordingly, by practicing the teachings of WO '374, addition of an unencapsulated antibiotic to a cyanoacrylate will cause the cyanoacrylate to prematurely cure (solidify), such that it cannot be applied to a wound in liquid form to seal the wound. Since the prematurely cured cyanoacrylate cannot seal the wound, it is also incapable of delivering the antibiotic to the wound in a controlled release manner. WO '394 does not properly teach or suggest liquid cyanoacrylate adhesives containing antibiotics – at most, it only teaches solid cured cyanoacrylate matrices containing antibiotics. Likewise, US '939 teaches antibiotics in microparticle or microcapsule form in a fluid carrier. The fluid cannot be a cyanoacrylate adhesive, however, because the carrier must have "a low solubility but a high permeability to the drug in question" – a cyanoacrylate adhesive is not permeable to the drug. The only cyanoacrylate disclosed is in the form of microparticle solid matrices containing active agent. Accordingly, the references, alone or in combination, do not teach preventing premature curing (polymerization and solidification) of the cyanoacrylate by the antibiotic.

As also discussed in the Declaration of Yong-Hua Zhu submitted with the response to the previous Office Action, the antibiotic in Applicants' adhesive maintains its antibiotic activity such that it can be delivered to the wound in a controlled release manner, unlike the antibiotic of

WO '374, which loses antibiotic activity due to reaction between the antibiotic and the cyanoacrylate. US '939 teaches controlled release of antibiotics, but does not specify which of the microencapsulation or microparticulate methods and materials are compatible with antibiotics and do not adversely impact their antibiotic activity. Accordingly, the references, alone or in combination, do not teach or suggest permitting controlled release of an antibiotic from a cured cyanoacrylate adhesive through defects in the cured adhesive provided by solvation of a defect forming agent.

Moreover, presence of a property not possessed by the prior art (*i.e.*, a liquid cyanoacrylate adhesive as claimed, compared to a solid cyanoacrylate matrix as disclosed in the prior art; antibiotic activity such that the antibiotic can be delivered to the wound in a controlled release manner, versus lost or impaired antibiotic activity) is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); MPEP § 716.02(a)(III). Accordingly, any *prima facie* case of obviousness would be rebutted.

For the above reasons, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 14, and 15 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of US 5,811,091 (hereinafter "US '091").

As discussed above, WO '374 and US '939, either alone or in combination, do not teach or suggest the invention as presently claimed. US '091 includes no additional disclosure overcoming the deficiencies of WO '374 and US '939. US '091 merely teaches that butyl cyanoacrylates and octyl cyanoacrylates can be employed adhesives for sealing wounds.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 10, 11, 14, 15, and 22-24 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of WO96/00760 (hereinafter "WO '760").

As discussed above, WO '374 and US '939, alone or in combination, do not teach or suggest the invention as presently claimed. WO '760 includes no additional disclosure overcoming the deficiencies of WO '374 and US '939. WO '760 merely discloses biomedical

adhesives comprising a biocompatible pH modifier (*e.g.*, a microencapsulated pH modifier).

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 6 and 18 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of WO99/20685 (hereinafter "WO '685").

As discussed above, WO '374 and US '939, alone or in combination, do not teach or suggest the invention as presently claimed. WO '685 includes no additional disclosure overcoming the deficiencies of WO '374 and US '939. WO '685 merely discloses coating formulations for sustained-release drug implants that include pore forming agents.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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